C. Remarks:

Upon entry of the amendments, claims 1-12, 19-25, and 51-55 will be pending in the application. Claims 13-18 and 26-50, which were previously withdrawn, are now canceled. Claims 1-3, 11, 19-20, and 51-53 have been amended for clarity and to correct typographical errors. Support for the amendments can be found throughout the Substitute Specification (*e.g.*, at least at ¶¶, 75-76). No new matter has been added.

Rejection under 35 U.S.C. § 102(b)

The Examiner maintains the rejection of claim 1-10, 12, and 52-55 as anticipated by U.S. Patent No. 5,785,965 ("Pratt"). According to the Examiner, these claims are being treated as similar to a product-by-process type claim for reciting the phrase "endothelial cells that have been genetically altered to express or over-express . . ." *See* Office Action, page 2. The Examiner contends that, because the endothelial cells used by Pratt already naturally express at least one cellular adherence factor, the claimed graft reads on the graft disclosed by Pratt. *See* Office Action, pages 3. Applicant traverses.

Claim 1 recites, in relevant part, an artificial vascular graft comprising a synthetic tubular element having a luminal surface coated with a plurality of endothelial cells that have been genetically transformed to express or over-express at least one endothelial cell proliferating growth factor and at least one cellular adherence factor. As indicated by claims 2-10 and 12, the graft can be made from a variety of material such as, for example, PTFE or ePTFE, and can have an inner cross-sectional area substantially equivalent to that of a blood vessel (*e.g.*, in the range from about 7 to about 700 mm^2). The endothelial cells can be obtained from a vein segment (of the intended recipient or otherwise), or other source (*e.g.*, bone marrow progenitor cells or

peripheral blood stem cells). The endothelial cells can be co-transfected with at least one growth factor (*e.g.*, VEGF, acidic or basic FGF, and HGF), and at least one adherence factor, or a portion of the cells can be transfected with at least one growth factor, while another portion is transfected with at least one adherence factor. The cells can also be transfected with at least one marker polypeptide. Once seeded on the luminal surface of the graft, the transfected endothelial cells form a confluent monolayer on the luminal surface.

Thus, claims 1-10 and 12 contain sufficient structural characteristics to define the invention as a product - even though the claims may recite a reference to how the product was made. *See In re Moore*, 439 F.2d 1232, 1236 (C.C.P.A. 1971). Thus, Applicant asserts that claims 1-10 and 12 are directed to a product and cannot be construed, in whole or in part, as product-by-process claims. That a process limitation appears in a product claim does not convert the claim to a product-by-process claim. *See Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983).

Similarly, claims 52-55 are directed to methods of replacing or bypassing at least a portion of a vascular system by implanting into the vascular system an artificial vascular graft comprising a synthetic tubular element having a luminal surface coated with a plurality of endothelial cells genetically transformed to express or over-express at least one proliferating growth factor and at least one cellular adherence factor. These claims are properly categorized as method of use claims, rather than product-by-process claims.

Notwithstanding the above, Applicant has herein amended claims 1, 2, 52, and 53 to recite that the endothelial cells have been genetically transformed with at least one sequence to express or over-express at least one endothelial cell proliferating growth factor, and with at least one sequence to express or over-express at least one cellular adherence factor. As described by

the Substitute Specification, when the endothelial cells obtained for use with the claimed invention do not naturally express at least one endothelial cell proliferating growth factor and/or at least one cellular adherence factor, then the cells are genetically transformed to express the factors with exogenous polynucleotide sequences that encode the desired factors. *See* specification at ¶ 0075. On the other hand, if the endothelial cells obtained for use with the claimed invention already naturally express at least one desired cell proliferating growth factor and/or at least one desired cellular adherence factor, then the cells are genetically transformed with sequences directed at causing the over-expression of the endogenously expressed factors (*e.g.*, by using additional copies of the endogenous gene or by using enhancer sequence elements). *See* specification at ¶¶ 0075-0076. Applicant contends that these amendments make clear that the claimed invention is distinct from that of Pratt. While Pratt does disclose a vascular prosthesis seeded with genetically transformed endothelial cells, the cells are only transformed with one sequence that is encoded to express VEGF. Pratt does not teach (or suggest) co-transforming the endothelial cells with a sequence specifically encoded to express or over-express a cellular adherence factor.

Accordingly, Applicant asserts that Pratt does not teach each and every limitation of claims 1-10, 12, and 52-55 as amended. Thus, Pratt cannot anticipate the claimed invention and this rejection should be withdrawn.

Rejection under 35 U.S.C. § 103(a).

The Examiner maintains the rejection of claims 11, 19-25, and 51 as obvious over Pratt in view of Nakamura, et al. (1999) J. Biol. Chem., 274(32): 22476-83 ("Nakamura"). According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time of

invention to make a vascular graft of ePTFE seeded with genetically transformed endothelial cells, as taught by Pratt, and that the cells could be transformed to express UP50, as taught by Nakamura, in order to promote the adhesion of endothelial cells. *See* Office Action, pp. 3-4. Applicant traverses the rejection as applied to the claims as currently presented. The declaration of Dr. Moshe Y. Flugelman is submitted herewith in support of the remarks and arguments stated *infra*.

Claim 11 depends directly from claim 1 and recites, in relevant part, an artificial vascular graft coated with a plurality of endothelial cells that have been genetically transformed with at least one sequence to express or over-express at least one endothelial cell proliferating growth factor and at least one sequence to express or over-express at least one cellular adherence factor, wherein the adherence factor is UP50 (also known as DANCE or Fibulin-5). While claims 19-25 and 51 are directed to methods of producing the artificial vascular graft and methods of producing the genetically transformed endothelial cells, respectively, claims 19-25 and 51 do not specifically recite genetically transformed endothelial cells that express or over-express UP50.

A rejection under 35 U.S.C. § 103 cannot be predicated on the mere identification of individual components of the claimed invention in the prior art. Rather, in order for an obviousness rejection to be proper, there must be a teaching or suggestion within the prior art that motivates the ordinarily skilled artisan at the time of invention to modify or combine the references to achieve the claimed invention with a reasonable expectation of success. These requirements are lacking here.

First, one of ordinary skill in the art would not have been motivated to combine the cited references to arrive at the inventions recited by independent claims 11, 19-25, and 51. Nor would one of ordinary skill in the art have been motivated to modify any of the references in a

manner required to meet the invention as recited by the present claims. Pratt is individually complete and functional in and of itself. In demonstrating an improved vascular graft seeded with genetically modified endothelial cells that facilitate rapid and complete endothelialization of the graft for increased patency and decreased intimal thickening, Pratt presents the results of implantation of a vascular graft in rabbits. Upon sacrifice of the rabbits at 8 hours, 14 days, and 28 days post-implant, Pratt observed that there was "no unusual adhesion, hematoma or seroma adhesion around the grafts." *See* Pratt, col. 12, lines 51-54. More importantly, Pratt indicates that the "grafts from all three groups were patent." *See id.* at lines 55-56. Thus, Pratt did not observe any problems with adhesion of the endothelial cells transformed with VEGF and seeded on the grafts. *See* Flugelman declaration, ¶ 7. In fact, by all indications Pratt teaches that the problems associated with incomplete endothelialization and subsequent denudation as a result of poor adhesion of cells due to sheer forces *in vivo* were solved by its invention. Thus, there would be no reason for one of ordinary skill in the art to modify the teachings of Pratt, or substitute elements from another reference, to achieve the claimed invention. *See* Flugelman declaration, ¶¶ 7-8.

Second, one of ordinary skill in the art at the time of invention would have concluded that the combination of Pratt and Nakamura would render Pratt unsatisfactory for its intended purpose, *i.e.*, to provide an improved vascular graft seeded with genetically modified endothelial cells that facilitate rapid and complete endothelialization of the graft. *See* Flugelman declaration, ¶¶ 9-10. While Nakamura does teach that DANCE promotes cell attachment via interaction of integrins and the RGD motif of the protein (*see* Nakamura, page 22477, col. 1, first paragraph), the reference must be considered as a whole. In its totality, Nakamura teaches that expression of UP50 prevents vigorous proliferation of endothelial cells in the lumen, because UP50 affects cell

growth as a "brake." *See* Nakamura at p. 22483, col. 1, fourth paragraph. Thus, the references teach away from the suggested combination. *See* Flugelman declaration, ¶¶ 9-10. Accordingly, one of skill in the art at the time of invention, upon reading Nakamura in view of Pratt would have been discouraged from following the path that was taken by Applicant in arriving at the claimed invention.

For the above reasons, Applicant asserts that the combination of Pratt and Nakamura is improper. Accordingly, the rejection of claims 11, 19-25, and 51 should be withdrawn.

Even if a *prima facie* case of obviousness has been made (and it has not), the weight of evidence from secondary considerations supports a conclusion of nonobviousness of the claimed invention.

First, as indicated by the instant specification, artificial vascular grafts are still not extensively used because they tend to lack long-term patency, *i.e.*, tend to occlude due to tissue in-growth and thrombosis. *See* specification, ¶ 0060. Furthermore, the problem has been addressed, unsuccessfully, by many in the field. *See id.* at ¶ 0006. Thus, there has been a long felt, but unresolved, need to provide an artificial vascular graft, wherein the endothelial cells can withstand the shear forces of blood flow *in vivo* such that long-term patency and prevention of tissue in-growth and thrombosis is achieved. Applicant's claimed invention satisfies this long felt yet unresolved need by transforming the endothelial cells seeded on the graft to express or over-express the cell adherence factor UP50 (with VEGF), thereby retaining endothelial cells under continuous shear stress, and preventing tissue in-growth and thrombosis of the graft. *See* specification, ¶ 0061 and Examples. Furthermore, the fact that those skilled in the relevant art

have not implemented the claimed invention, despite its great advantages, indicates that the claimed invention is not obvious.

Second, the claimed invention is contrary to the teachings of the prior art, as one of skill in the art at the time of invention trying to increase graft patency and lifetime by preventing neointimal proliferation and thrombosis would not have reasonably expected to achieve this objective by seeding the graft according to the claimed invention. As indicated by the instant application, complete endothelialization is desirable as it prevents thrombosis and overgrowth of smooth muscle cells, which are responsible for the secretion of most of the extracellular matrix and which leads to undesirable tissue in-growth into the graft lumen leading to graft narrowing and occlusion. *See* specification, ¶¶ 0004 and 0010. Accordingly, seeding the graft with endothelial cells which encode a partial inhibitor (UP50) to cell growth would have been contrary to accepted wisdom at the time of invention, because one of skill in the art at the time of invention would have believed that a partial inhibitor of cell growth would prevent endothelialization of the graft. *See* Flugelman declaration at ¶ 11.

Finally, the artificial vascular grafts of the claimed invention possesses superior and unexpected properties over the grafts taught by the prior art. As Flugelman indicates, in grafts seeded with endothelial cells transformed with VEGF alone (as in Pratt), there is increased detachment of the endothelial cells from the inner surface of the graft upon exposure to flow (as compared to grafts seeded with endothelial cells expressing or over-expressing UP50 alone or in combination with VEGF). *See* Flugelman declaration at ¶ 12 and accompanying data. As Flugelman further indicates, in grafts seeded with endothelial cells transformed with UP50 and VEGF, VEGF had a surprisingly synergistic effect on endothelial cell proliferation by increasing proliferation to a level superior to endothelial cells transformed with VEGF alone. The partial

inhibitory effect of UP50 on endothelial cell proliferation was thereby reversed upon addition with exogenous VEGF or by endothelial cells co-transformed with VEGF. *See* Flugelman declaration, ¶¶ 12-13 and accompanying data. In contrast, partial inhibition of smooth muscle cell proliferation by UP50 is not reversed by the addition of a growth factor such as bFGF. *See id.*, ¶¶ 14-15 and accompanying data. This finding is particularly significant because, as noted by Flugelman, bFGF is a strong mitogenic growth factor for smooth muscle cells and is abundantly present at vascular injury cites. *See id.* Accordingly, the result is a superior vascular graft that has the surprising ability to selectively permit rapid endothelialization and maintain the proliferative capacity of endothelial cells while inhibiting smooth muscle cell proliferation, thereby increasing graft patency and preventing neointimal formation and thrombosis.

For all of the foregoing reasons, and in view of the amendments to the claims, Applicant respectfully requests reconsideration and withdrawal of the rejections under § 103(a).

D. Conclusion:

Applicant submits that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

The Commissioner is hereby authorized to charge payment of any additional fees that may be required in connection with these papers, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 24558-501.

Respectfully submitted,

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